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Endoscopic endonasal transsphenoidal surgery for functional pituitary adenomas

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Object. The purpose of this study was to analyze preoperative predictors of endocrinological remission following endonasal endoscopic resection of therapy-resistant prolactin-, growth hormone (GH)–, and adrenocorticotropic hormone (ACTH)–secreting pituitary adenomas and to establish benchmarks for cure by using the most recent consensus criteria.

Methods. The authors reviewed a prospective database of 86 consecutive functional pituitary adenomas that were resected by a purely endoscopic endonasal transsphenoidal technique. Extent of resection was evaluated on postoperative contrast-enhanced MR imaging. Endocrinological remission was defined according to the most recent consensus criteria.

Results. The majority of functional adenomas (62.8%) were classified as macroadenomas (> 1 cm in maximum diameter), and 20.9% of lesions had invaded the cavernous sinus (CS) at the time of surgery. A gross-total resection was achieved in 75.6% of all patients. The rate of endocrinological remission differed between various types of functional adenomas. Cure rates were 92.3% (microadenomas) and 57.1% (macroadenomas) for prolactinomas, 75% (microadenomas) and 40% (macroadenomas) for GH-secreting tumors, and 54.5% (microadenomas) and 71.4% (macroadenomas) for ACTH-secreting tumors. Lower rates of cure occurred in GH-secreting macroadenomas due to a high rate of CS invasion, and in ACTH-secreting adenomas due to a high rate of lesions that were not visible on preoperative MR imaging. Whereas univariate analysis showed that macroadenoma, suprasellar, cavernous extension, or extent of resection correlated with cure, on multivariate analysis, only extent of resection and suprasellar extension predicted cure. One patient developed postoperative meningitis that was complicated by hydrocephalus requiring a ventriculoperitoneal shunt. Two patients developed postoperative panhypopituitarism, and 2 patients suffered from CSF leaks, which were treated with lumbar CSF diversion.

Conclusions. This paper reports benchmarks for endocrinological cure as well as complications in a large series of purely endoscopic pituitary surgeries by using the most recent consensus criteria. The advantages of extended endonasal approaches are most profound in tumors with suprasellar extension and CS invasion.
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Key Words • **endoscopy** • **acromegaly** • **prolactinoma** • **Cushing disease** • **minimally invasive surgery** • **transsphenoidal surgery** • **skull base**

The transsphenoidal approach for resection of a pituitary adenoma was first performed by Herman Schloffer more than 100 years ago.[37] Subsequently, the transsphenoidal approach created great interest, and a variety of modifications of this approach were described shortly thereafter. As discussed in a report by Henderson,[18] Harvey Cushing was the first to present a large clinical series of 231 transsphenoidal pituitary adenoma resections in 1939. However, because lack of adequate preoperative imaging made it impossible to foretell the size and configuration of the adenomas, he abandoned the procedure in favor of transcranial approaches. The majority of neurosurgeons followed Cushing's lead, and it was not until the advent of 2 technological milestones that the transsphenoidal technique resurfaced. First, the development of imaging techniques such as CT and MR imaging provided accurate information about the size and location of a lesion and allowed for appropriate patient selection and determination of the appropriate surgical access. Second, the introduction of the operating microscope and later endoscopy greatly improved intraoperative illumination and visualization. Although there are numerous studies reporting the endocrinological outcome following microsurgical

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; CS = cavernous sinus; GH = growth hormone; GKS = Gamma Knife surgery; GTR = gross-total resection; IGF-I = insulin-like growth factor–I; PRL = prolactin.

transsphenoidal resection of functional pituitary adenomas,[1,4–7,11,15,17,20,21,23,25,26,28,29,31,33,34,39,41,43–46] there is a paucity of literature reporting the endocrinological outcome following use of a purely endoscopic transsphenoidal technique.[8,12,19,36] Moreover, continuous re-evaluation of endocrinological outcomes following surgical treatment of functional pituitary lesions is necessary to keep up with the latest definitions of postoperative endocrinological remission. Based on improvements in follow-up data, criteria for endocrinological remission following resection have constantly evolved over time. Here we present our single-center experience in which we used the latest criteria for an endocrinological cure for PRL-, GH-, and ACTH-secreting adenomas[3,9,16] in a cohort treated with a purely endoscopic endonasal transsphenoidal technique.

Methods

Patient Demographic Data

We analyzed a prospectively collected database of all patients who underwent endoscopic endonasal surgery for a functional pituitary adenoma at Weill Cornell Medical College, New York–Presbyterian Hospital between February 2004 and June 2010, as a collaboration between the departments of Neurosurgery and Otolaryngology. Functional tumors were resected by the senior authors (T.H.S. and J.A.B.) using a purely endoscopic endonasal transsphenoidal approach. This study was approved by the institutional review board. For each operation, the duration of surgery, estimated blood loss, relevant laboratory values, adjuvant treatments, and complications were recorded.

Radiographic Evaluation

Prior to resection, all patients underwent contrast-enhanced MR imaging. Tumor invasion of the CS was defined according to the following criteria: three-quarters or more encasement of the internal carotid artery, obliteration of the carotid sulcus venous compartment, or crossing of the lateral intercarotid line by the tumor.[10] Routinely, the surgical site was analyzed by contrast-enhanced MR imaging on postoperative Day 1, 3 months after surgery, and then at yearly intervals.

Surgical Technique

Prior to surgery, all patients received antibiotics and glucocorticoids, and intrathecal fluorescein was used in 73% of cases to label CSF.[32] We use Brainlab neuronavigation for all of our cases. A detailed description of the procedure has been published previously.[19,24,35,38] Briefly, after application of topical cocaine to the nasal mucosa, the mucosa of the middle turbinates is infiltrated with a mixture of 1% lidocaine and epinephrine (1:100,000). The sphenoid ostia are identified bilaterally and enlarged by removal of bone. We then use a tissue shaver to resect the posterior third of the nasal septum. Using a high-speed drill and curettes, the anterior wall of the sella is opened. We attempt to resect microadenomas en bloc, whereas macroadenomas are first internally decompressed by removing the inferior portion of the tumor, followed by resection of the lateral portions. This maneuver prevents the suprasellar arachnoid from herniating down into the sella. Resection of extensive suprasellar components may require an extended approach to the lesions, including removal of the tuberculum sellae and planum sphenoidale.[24] Tumor is dissected off the medial CS wall. In case of CS invasion, the dura mater is opened medial to the internal carotid artery, and tumor can be easily removed from this area. Although it is also possible to open the CS lateral to the carotid, one must carefully weigh the safety of this maneuver with the increased extent of resection that it will facilitate, and how this will affect the long-term outcome of the patient, compared with treatment with stereotactic radiosurgery. The skull base defect is closed in a multilayered fashion.[27]

Endocrinological Evaluation

All patients underwent pre- and postoperative endocrinological evaluation for free cortisol, ACTH, free thyroxine, thyroid-stimulating hormone, PRL, GH, IGF-I, testosterone, estradiol, luteinizing hormone, and follicle-stimulating hormone to assess for endocrinological derangements (except for 1 patient, who was lost to endocrinological follow-up). The diagnosis of a prolactinoma was made based on serum PRL levels of > 150 ng/ml in combination with typical clinical symptoms.[9] In patients with prolactinoma, endocrinological remission was defined as postoperative PRL levels of < 20 ng/ml in females or < 15 ng/ml in males. The diagnosis of Cushing disease was based on either abnormal 24-hour urinary free cortisol or abnormal results on low-dose dexamethasone suppression tests, defined as failure of 1 mg of dexamethasone to reduce plasma cortisol levels to < 1.8 μg/ml the next morning.[3,30] In Cushing disease, endocrinological remission was defined as an early morning cortisol level measurement of ≤ 1.8 μg/ml obtained within 48 hours after surgery or a normalization of the 24-hour urinary free cortisol.[3] The diagnosis of acromegaly was based on abnormal basal fasting levels of GH and IGF-I.[16] Biochemical remission was defined as a normal IGF-I level combined with a glucose-suppressed GH level of ≤ 0.4 ng/ml, or alternatively, combined with a basal GH level of ≤ 1 ng/ml. The IGF-I level was always evaluated according to age-adjusted diagrams.[16]

Statistical Evaluation

Continuous variables are shown as the mean values ± the SEM and the range. Categorical values are shown as percentages. Continuous variables between patients with prolactinomas, acromegaly, or Cushing disease were analyzed by ANOVA, followed by a Tukey post hoc test. Tumor diameter between cured and noncured patients was assessed using a Mann-Whitney U-test. Binary logistic regression was used to determine the effect of extent of resection, tumor size, suprasellar extension, and invasion of the CS on endocrinological remission. A conditional backward stepwise method was used to calculate a multivariate logistic regression model. Preoperative and postoperative hormone levels in serum were assessed using a paired Student t-test. A p value < 0.05 was considered significant. Statistical analyses were performed using SPSS software (version 18.0 for Macintosh).

Results

Overall Patient Characteristics

At total of 86 patients underwent resection of functional pituitary adenomas in which a purely endoscopic transsphenoidal technique was used. The cohort was composed of 37 male and 49 female patients with a mean age of 45.2 years (range 12–82 years; Table 1). Our series contains 35 patients with prolactinomas, 18 with Cushing disease, and 33 with GH-secreting adenomas. The majority of patients (85%) who underwent resection sought medical attention for symptoms related to excess hormone production. The remaining patients complained of severe headaches (4.7%), diplopia (3.5%), or vision loss (10.5%). Patients with diplopia and vision loss had significantly larger adenomas compared with the rest of the cohort (3.3 cm and 2.6 cm, respectively, vs 1.2 cm maximum tumor diameter; $p < 0.001$). In patients with loss of vision, visual field testing revealed bitemporal defects in 3 patients, binasal defects in 1 patient, or hemianopia in 2 patients. One-third of patients with acute vision loss where found to have pituitary apoplexy on MR imaging. The remaining 2 patients with apoplexy presented with acute onset of severe headaches. In our cohort, 20.9% of patients had undergone a previous resection. Preoperative MR imaging revealed macroadenomas (maximum diameter > 1 cm) in two-thirds of our patients. Invasion of the CS was present in 20.9%, and suprasellar tumor extension was detected in 29.1%. Whereas the pituitary–hypothalamic axis was intact in the majority of patients (89.5%), 6 patients were found to have hypogonadism, 2 had hypothyroidism, and 1 suffered from both panhypopituitarism and diabetes insipidus prior to surgery.

Surgical Results

Endoscopic endonasal transsphenoidal procedures lasted an average of 167.3 minutes (range 79–380 minutes). The mean estimated blood loss was 133.1 ml (range 20–900 ml) for all procedures in this cohort. Significant suprasellar tumor extension required an extended transsphenoidal approach in 5 patients (5.8%). Labeling of CSF by intrathecal fluorescein revealed intraoperative CSF leaks in 47% of procedures. As expected, adenomas with intraoperative CSF leaks had a significantly larger diameter compared with the remaining adenomas (1.9 cm vs 1.2 cm, $p < 0.01$). The skull base defect was closed in a multilayered fashion with vomer (28%), Porex (4%), fat (57%), fascia lata (4%), and DuraSeal (83%). A nasoseptal flap was used in 7 patients, the majority of whom had intraoperative CSF leaks. Moreover, tumors that required nasoseptal flaps had a significantly larger diameter than tumors in which no flap was used (2.5 cm vs 1.4 cm, $p < 0.05$). Postoperative imaging revealed a GTR in 75.6% of all patients in our cohort (Table 2). The rate of GTR was 90.6% for microadenomas and 66.7% for macroadenomas. Once functional adenomas had invaded the CS, the rate of GTR decreased to 33.3%. Thus, invasion of the CS was a significant negative predictor for GTR (OR

TABLE 1: Characteristics in 86 patients with functional pituitary adenomas

Characteristic	Total	Type of Pathology		
		PRL-Secreting	ACTH-Secreting	GH-Secreting
no. of patients	86	35	18	33
sex				
M	37 (43.0%)	13 (37.1%)	5 (27.8%)	19 (57.6%)
F	49 (57.0%)	22 (62.9%)	13 (72.2%)	14 (42.4%)
mean age in yrs (± SEM)	45.2 ± 1.8	36.3 ± 2.5*	53.8 ± 3.8	49.9 ± 2.6
previous op				
yes	18 (20.9%)	8 (22.9%)	6 (33.3%)	4 (12.1%)
no	68 (79.1%)	27 (77.1%)	12 (66.6%)	29 (87.9%)
max tumor diameter				
<1 cm	32 (37.2%)	13 (37.1%)	11 (61.1%)	8 (24.2%)
>1 cm	54 (62.8%)	22 (62.9%)	7 (38.9%)	25 (75.8%)
invasion of CS				
yes	18 (20.9%)	5 (14.3%)	3 (16.7%)	10 (30.3%)
no	68 (79.1%)	30 (85.7%)	15 (83.3%)	23 (69.7%)
suprasellar extension				
yes	25 (29.1%)	14 (40.0%)	3 (16.7%)	8 (24.2%)
no	61 (70.9%)	21 (60.0%)	15 (83.3%)	25 (75.8%)
apoplexy				
yes	5 (5.8%)	5 (14.3%)	0 (0.0%)	0 (0.0%)
no	81 (94.2%)	30 (85.7%)	18 (100.0%)	33 (100.0%)

* Significant according to ANOVA ($p < 0.001$) and the Tukey post hoc test ($p < 0.01$) compared to GH-secreting lesions; $p < 0.001$ compared to ACTH-secreting adenomas.

TABLE 2: Outcome in 86 patients with functional pituitary adenomas*

Characteristic	Total	Type of Pathology		
		PRL-Secreting	ACTH-Secreting	GH-Secreting
no. of patients	86	35	18	33
GTR				
yes	65 (75.6%)	26 (74.3%)	13 (72.2%)	26 (78.8%)
no	21 (24.4%)	9 (25.7%)	5 (27.8%)	7 (21.2%)
EC	85†			
yes	51 (60.0%)	24 (70.6%)	11 (61.1%)	16 (48.5%)
no	34 (40.0%)	10 (29.4%)	7 (38.9%)	17 (51.5%)
EC in microadenomas	32			
yes	24 (75.0%)	12 (92.3%)	6 (54.5%)	6 (75.0%)
no	8 (25.0%)	1 (7.7%)	5 (45.5%)	2 (25.0%)
EC in macroadenomas	53			
yes	27 (50.9%)	12 (57.1%)	5 (71.4%)	10 (40%)
no	26 (49.1%)	9 (42.9%)	2 (28.6%)	15 (60.0%)
EC in adenomas w/ CS invasion	18			
yes	7 (38.9%)	3 (60.0%)	1 (33.3%)	3 (30.0%)
no	11 (61.1%)	2 (40.0%)	2 (66.7%)	7 (70.0%)
GKS				
yes	12 (14.0%)	3 (8.6%)	4 (22.2%)	5 (15.2%)
no	74 (86.0%)	32 (91.4%)	14 (77.8%)	28 (84.8%)
mean time of last FU in mos (± SEM)	22.8 ± 2.2	22.3 ± 3.4	24.8 ± 5.1	22.2 ± 3.9

* EC = endocrinological cure; FU = follow-up.

† One patient was lost to endocrinological follow-up.

0.076, $p < 0.001$; 95% CI 0.023–0.255), whereas tumor diameter and suprasellar extension were not predictors of extent of resection. The average hospital stay was 4.3 days (range 2–32 days). The average length of the follow-up period from resection to laboratory testing was 22.8 months (range 1–76 months; Table 2).

Prolactinomas. In the current series, 35 patients with PRL-secreting adenomas underwent an endoscopic transsphenoidal tumor resection (Table 1). The mean age of this group was 36.3 years (range 12–73 years), and it was composed of 22 female and 13 male patients. Those with prolactinomas were significantly younger compared with patients with GH- or ACTH-secreting adenomas ($p < 0.001$). The majority (80%) of these patients had attempted medical therapy to control excess PRL secretion. Medical therapy failed for 3 main reasons: 1) insufficient control of excess hormone secretion (12 patients); 2) enlargement of the pituitary adenoma despite maximum medical therapy (5 patients); and 3) intolerable adverse medication effects (11 patients). Seven patients with PRL-secreting adenomas underwent resection without a trial of medical therapy. Five of these patients presented with acute vision loss, and 2 presented with severe headaches, of which apoplexy was the cause in 5 patients. All adenomas complicated by apoplexy were prolactinomas. Analysis of preoperative imaging revealed an average maximum diameter of 1.5 cm (range 0.4–4 cm). Thus, 62.9% of prolactinomas were classified as macroadenomas. Endoscopic endonasal transsphenoidal surgery resulted in a GTR in 74.3% of patients with PRL-secreting adenomas (Table 2). Similarly, 70.6% of patients with prolactinomas achieved endocrinological remission. Of the 24 cured patients, 1 required additional GKS. Resection led to a significant reduction of immediate postoperative ($p < 0.05$) and last follow-up ($p < 0.001$; Table 3) serum PRL levels compared with preoperative levels. Of 29 patients with prolactinomas who had an intact pituitary–hypothalamic

TABLE 3: Endocrinological outcome in 86 patients with functional pituitary adenomas

Outcome	Hormone Level				
	PRL (ng/ml)	ACTH (pg/ml)	Cortisol (mg/ml)	GH (ng/ml)	IGF-I (ng/ml)
excess serum hormone levels					
preop	684.9 ± 308.4	85.4 ± 19.1	16.5 ± 4.2	30.3 ± 8.2	833.5 ± 56.5
postop	107.9 ± 50.1	42.0 ± 18.2	13.6 ± 4.3	3.9 ± 1.2	469.7 ± 42.5
at last FU	34.1 ± 11.8	45.0 ± 14.4	9.8 ± 2.0	2.3 ± 0.9	295.6 ± 40.1

axis preoperatively, 24 remained intact. Two patients developed new hypothyroidism, 2 had hypogonadism, and 1 had diabetes insipidus.

Cushing Disease. Our cohort included 18 patients in whom Cushing disease was diagnosed based on endocrinological and clinical evaluation (Table 1). Patients with Cushing disease were on average 53.8 years old (range 25–82 years). There were 13 female and 5 male patients. The gross majority of patients (72.2%) with ACTH-producing adenomas presented with classic cushingoid symptoms. Two patients received the diagnosis of Cushing disease during the workup for intractable hypertension, and 1 patient during the workup for diplopia. Analysis of preoperative imaging revealed an average maximum tumor diameter of 0.8 cm (range 0–2.3 cm). The ACTH-secreting adenomas were significantly smaller compared with both PRL- ($p < 0.05$) and GH-secreting ($p < 0.01$) adenomas. Thus, only 38.9% of ACTH-secreting adenomas were classified as macroadenomas. No distinguishable pituitary pathological features could be identified on preoperative MR imaging in 4 patients. These patients underwent exploration of the pituitary gland without further prior workup, and endocrinological remission was achieved in 2 of these 4 patients. Two patients did not achieve biochemical remission according to our criteria. One of them has ACTH and serum cortisol levels that remain consistently within normal limits 33 months after the procedure, whereas the other patient had good relief of his symptoms for 6 years, but eventually suffered from a recurrence requiring repeat resection, resulting again in alleviation of his excess cortisol production. Endoscopic endonasal transsphenoidal surgery resulted in GTR in 72.2% of patients with Cushing disease (Table 2). However, only 61.1% of patients achieved endocrinological cure. Biochemical remission rates were 50% in patients with lesions that were not visible on preoperative imaging, 54.5% in all microadenomas, and 71.4% in macroadenomas. Of 11 patients with ACTH-secreting adenomas that were cured, 2 underwent GKS. Endoscopic endonasal transsphenoidal resection led to a significant reduction of postoperative ACTH levels in serum compared with preoperative serum levels ($p < 0.05$; Table 3). Of 16 patients with Cushing disease who had an intact pituitary–hypothalamic axis preoperatively, 4 developed defects in one axis.

Growth Hormone–Producing Adenomas. A total of 33 patients suffered from excess GH secretion (Table 1). This cohort consisted of 14 female and 19 male patients, and the average age was 49.9 years (range 20–77 years). Two-thirds of patients with GH-producing adenomas presented with classic acromegalic symptoms. Four GH-secreting adenomas were diagnosed incidentally, 2 patients sought medical attention for headaches, and 1 patient each sought help for complaints of bone pain, joint pain, diplopia, amenorrhea, or sleep apnea. Evaluation of GH-secreting adenomas on preoperative MR imaging revealed an average maximum diameter of 1.7 cm (range 0.6–4 cm). Thus, 75.8% of patients with acromegaly had macroadenomas, and 30.3% of GH-secreting adenomas had invaded the CS. A GTR was achieved in 78.8% of patients, and 48.5% fulfilled criteria for endocrinological cure (Table 2). Biochemical cure was achieved in 75% of GH-secreting microadenomas, whereas the rate was lower in macroadenomas (40%) due to a high proportion of tumors with invasion of the CS. Of 17 patients who achieved endocrinological remission, 2 underwent GKS. Endoscopic endonasal transsphenoidal resection led to a significant reduction of GH levels in serum immediately postoperatively ($p < 0.01$) as well as at last follow-up ($p < 0.05$) compared with preoperative levels (Table 3). A significant reduction of serum levels of IGF-I was also observed postoperatively ($p < 0.001$) as well as at the last follow-up ($p < 0.001$) compared with preoperative serum levels. Of 32 patients with GH-secreting adenomas who had an intact pituitary–hypothalamic axis preoperatively, 2 suffered from panhypopituitarism and 2 from hypogonadism following endoscopic endonasal transsphenoidal resection.

Predictors for Endocrinological Remission

Adenomas allowing for endocrinological remission had a significantly smaller diameter compared with lesions that were not cured (1.2 cm vs 1.8 cm, respectively; $p < 0.05$; Fig. 1). Accordingly, univariate logistic regression identified GTR, a maximum adenoma diameter of < 1 cm, lack of suprasellar extension, and lack of CS in-

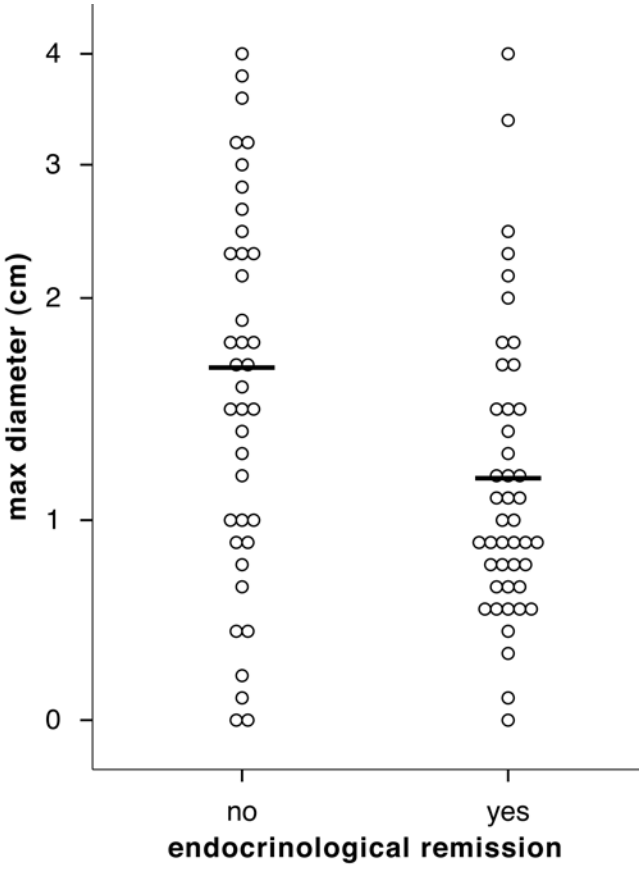

Fig. 1. Graph showing association of tumor size with endocrinological remission. Adenomas that allow for biochemical cure by endoscopic transsphenoidal resection have a significantly smaller maximum diameter on univariate analysis compared with the remaining adenomas ($p < 0.05$). *Horizontal bars* indicate the mean values.

TABLE 4: Predictors for endocrinological cure in 86 patients with functional pituitary adenomas*

	Univariate Analysis			Multivariate Analysis		
Adenoma Characteristics	OR	p Value	95% CI	OR	p Value	95% CI
GTR	4.40	0.006	1.54–12.57	3.95	0.013	1.344–11.63
no suprasellar extension	3.23	0.017	1.23–8.52	2.86	0.042	1.040–7.856
microadenoma	2.89	0.031	1.10–7.58		NS	
no CS invasion	3.01	0.044	1.03–8.80		NS	

* NS = not significant.

vasion as positive predictors for endocrinological cure (Table 4). When combining these significant predictors in a multivariate analysis, only GTR and suprasellar tumor extension remained significant independent predictors for biochemical remission.

Postoperative Complications

There was no operative or perioperative death in this cohort. There was 1 case of meningitis leading to hydrocephalus requiring a shunt (Table 5). Two patients developed postoperative CSF leaks, which were treated with 4 days of CSF diversion via lumbar drainage. Two patients developed sinusitis after the surgery. One patient complained of a unilateral dry eye requiring treatment with artificial tears.

Discussion

In this series of patients, we present endocrinological outcome according to the most recent updated criteria for endocrinological cure following a purely endoscopic endonasal transsphenoidal surgery for functional pituitary adenomas. The criteria for endocrinological cure have evolved over the last decades, and until now there has been little universal consensus. The use of different criteria makes comparisons of endocrinological outcomes between different surgical series difficult. For the current series we used the latest consensus criteria for diagnosis of postoperative endocrinological remission for acromegaly, Cushing disease, and prolactinomas.[3,9,16] Because the endoscopic technique constitutes the latest refinement of transsphenoidal surgery,[40] a comparison of our results with a standard microscopic transsphenoidal technique was performed.

In our series endocrinological cure was achieved for 70.6% of PRL-secreting adenomas. This is similar to the weighted average cure rate (62%) derived from several microscopic series.[29,33,39,43] It is obvious that the value of this comparison is limited due to heterogeneities of adenoma size and invasiveness, follow-up times, and definition of endocrinological cure. However, it further corroborates previous claims of equal efficiency of endoscopic technique for achieving biochemical cure in PRL-secreting adenomas.[12,14] In a study of endoscopic transsphenoidal surgery by Dehdashti and colleagues,[12] the same criteria for endocrinological cure for PRL-secreting adenomas were used as in the current series (Table 6). However, adenoma characteristics are quite different. In the current series, 8.6% of PRL-secreting adenomas required an extended approach for appropriate access to suprasellar portions, whereas adenomas that required extended approaches were excluded by Dehdashti et al. Moreover, the rate of CS invasion was higher in the current series (14.3%) compared with the aforementioned study (8%). This may explain the slightly higher biochemical cure rate (88%) reported by Dehdashti and colleagues for their 25 prolactinomas. The second published series reporting endocrinological outcome following endoscopic transsphenoidal adenoma resection has a patient cohort that appears to be more similar to ours.[14] Despite endocrinological criteria that were not as stringent as in our series (maximum serum PRL level for female patients was 30 ng/ml, compared with 20 ng/ml in the current series), the cure rate for Frank and colleagues[14] (75.7%) is similar to the rate achieved in our series. Endoscopic transsphenoidal resection yielded endocrinological cure rates above 85% for PRL-secreting microadenomas in both studies[12,14] as well as in the current series. Endocrinological remission rates for PRL-secreting adenomas with invasion of CS differ among the series. Whereas Frank and colleagues report a cure rate (36.5%) that is comparable to the current series (60.0%), Dehdashti and colleagues do not report cures in patients with this type of lesion.

For ACTH-secreting adenomas an average cure rate of

TABLE 5: Complications in 86 patients with functional pituitary adenomas

Type of Complication	No. of Patients (%)	Treatment
meningitis & communicating hydrocephalus	1 (1.2)	antibiotics & ventriculoperitoneal shunt
CSF leak	2 (2.3)	lumbar CSF diversion
panhypopituitarism*	2 (2.3)	hormone replacement
sinusitis	2 (2.3)	antibiotics
dry eye	1 (1.2)	artificial tears

* In patients with intact pituitary–hypothalamic axis preoperatively.

TABLE 6: Literature review of endocrinological remission following transsphenoidal surgery*

	PRL-Secreting			ACTH-Secreting			GH-Secreting			
Authors & Year	No. of Pts	GTR	EC	No. of Pts	GTR	EC	No. of Pts	GTR	EC	FU (mos)
Frank et al., 2006	66	NA	75.7%	56	NA	67.8%	83	NA	69.0%	54.0
Dehdashti et al., 2008	25	92.0%	88.0%	27	85.0%	81.0%	34	85.0%	71.0%	19.0
present study	35	74.3%	70.6%	18	72.2%	61.1%	33	78.8%	48.5%	22.8

* NA = not available; Pts = patients.

78% is reported in the major microscopic series.[4,7,17,21,41,46] In our series endocrinological remission was achieved in 61.1% of patients. A low rate of cure (50%) was detected in adenomas that were obscure on preoperative imaging. Moreover, endocrinological cure was achieved in only 40% of patients with visible adenomas of < 5-mm diameter on preoperative MR imaging, whereas endocrinological cure was obtained in 100% of microadenomas > 5 mm. Poor preoperative visualization of ACTH-secreting adenomas is a well-documented poor prognostic factor for endocrinological remission.[6] Accordingly, we detected lower cure rates in ACTH-secreting microadenomas compared with those reported in studies by Frank et al.[14] and Dehdashti et al.[12] (54.5%, 67.7%, and 100%, respectively), whereas the cure rates for macroadenomas were comparable (71.4%, 62.5%, and 68%, respectively).

The current literature on microscopic transsphenoidal resection of GH-secreting adenomas suggests an average cure rate of approximately 67%.[1,15,23,31,44,45] In the current study endocrinological remission was achieved in only 51.5% of GH-secreting adenomas. The rate of biochemical cure for GH-secreting microadenomas was 75% in the current series, and thus was similar to the rates reported by Frank and colleagues[14] (83%) as well as by Dehdashti and colleagues[12] (83%). Given the large proportion of GH-secreting macroadenomas that had invaded the CS, it is not surprising that we detected lower cure rates in GH-secreting macroadenomas compared with studies by Frank et al. and Dehdashti et al. (40%, 64.5%, and 70.1%, respectively).

The current patient cohort includes a great proportion of adenomas with invasion of the CS (20.9%). Using a microsurgical transsphenoidal approach, Kitano and colleagues[22] report a 67% rate of endocrinological remission in 12 patients with GH-secreting pituitary adenomas invading the CS. Kitano and colleagues used a microscopic endoscope-assisted transsphenoidal technique to reach tumors that had invaded the CS. The mean blood loss was approximately 1000 ml, compared with approximately 132 ml for tumors with CS invasion in our current cohort. Kitano and colleagues report a 26% rate of transient extraocular palsy, whereas this complication did not occur in the current series. The aggressiveness used to achieve resection of intracavernous tumor varies in the endoscopic literature. Whereas in one recent endoscopic series the investigators did not attempt resection of tumor from the CS,[12] Frank and Pasquini[13] report endocrinological remission in 43% of functional tumors with invasion of the CS resected using the endoscopic technique. A similar rate of cure was achieved in the current series (38.9%). It is our opinion that one must balance risk with benefit when operating in the CS, and it may be preferable to control residual tumor with stereotactic radiosurgery rather than to achieve GTR associated with a risk morbidity.

A potential limitation of the current study is the relatively short follow-up time of 22.8 months. The occurrence of late recurrences following resection of functioning adenomas in patients with assumed endocrinological cure is well established.[2,17,42,46] These recurrences have been the main motivation to introduce more and more stringent criteria for endocrinological cure. Early results from recent endoscopic series[12,14] as well as the current study, in which no recurrences were observed in patients who achieved endocrinological remission, are encouraging. However, continued monitoring of these patient cohorts is required to eventually provide long-term endocrinological remission rates following endoscopic resection of functional pituitary adenomas.

Conclusions

An endoscopic transsphenoidal resection of functional pituitary adenomas leads to endocrinological remission in 60% of patients. Importantly, our treatment regimen of endoscopic resection in combination with GKS for possible residual disease allows for endocrinological remission in a significant proportion of functional adenomas with CS invasion as well as in recurrent adenomas, while minimizing procedure-related morbidity.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Schwartz, Hofstetter. Acquisition of data: Hofstetter, Shin, Mubita. Analysis and interpretation of data: Schwartz, Hofstetter. Drafting the article: Hofstetter, Shin. Critically revising the article: Schwartz, Huang, Boockvar, Anand. Reviewed final version of the manuscript and approved it for submission: Schwartz. Statistical analysis: Hofstetter.

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